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EDITORIAL

Injury and Repair in the Immature Brain

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The articles in this special issue of *Translational Stroke Research* focus on injury and repair in the developing brain. An appropriate question might be raised at the outset—why address an issue, including 13 papers, to the problem of injury and repair particularly on the immature brain when there is such a wealth of information available on this topic for the adult brain? The answer is simply that mechanisms of injury and strategies for repair often are very different in the immature as compared with the adult brain [1, 2]. A tentative pipeline is presented for development of neuroprotective agents for perinatal brain injury. The issue covers different aspects of endogenous and extrinsic stem cells, angiogenesis, neuroprotection, immune responses, and biomarkers. Each article is written by experts in the field and is well organized, clear, and informative. This special issue is extraordinarily timely and of value to neonatologists, neurologists, pediatricians, fetal medicine specialists, and neuroscientists with an interest in translational research.

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The special issue includes four papers on stem cells in the immature brain. Phillips et al. [3] offer an update on predominately preclinical studies using extrinsic embryonic, cord blood, and mesenchymal stem cells in immature brain injury models. It is pointed out that these interventions can provide beneficial effects but can also be associated with significant risks. Misumi et al. propose a seven-step culture method to produce oligodendroglial cells from induced pluripotent stem cells [4], and it will be interesting in the future to see if these cells can promote myelination in animal models. Another strategy is to pharmacologically influence endogenous stem and progenitor cells. For example, vascular endothelial growth factor (VEGF) C seems to promote oligodendrocyte development and stimulate myelination via VEGF receptor 3, according to elegant work by Bain et al. [5]. Furthermore, Doycheva et al. found that cotreatment with granulocyte colony-stimulating factor and stem cell factor conferred significant neuroprotection in neonatal rats [6], suggesting that administration of factors regulating stem and progenitor cells not only prevents brain atrophy but may also improve neurological function.

So far, studies on the role of the vascular bed in immature injury are limited, in spite of the well-acknowledged importance of the vascular stem cell niche. Fernandez-Lopez et al. [7] propose that suppressed angiogenesis after stroke, in contrast to what is reported in models of brain injury in adult animals, may limit recovery, and Dzietko et al. [8] demonstrate that VEGF (administered as late as 1 week after the insult!) has neuroprotective effects, probably acting at least partly through improvement of vascular development. The importance of the vascular response is also supported by Zhu et al. [9] who find that inhaled nitric oxide offers neuroprotection in male, but not female, mice, probably via increased circulation to the penumbral region at risk. This is a novel mechanism recently described in models of adult brain injury, now also verified in the immature brain.

Inflammation is considered to be important in brain injury, but the relative contribution of peripheral vs. CNS immune cells remains incompletely understood. In this issue, Fathali et al. provide support that NK cells may participate in brain injury, as CD161 knockdown and splenectomy reduced brain injury and improved neurobehavior in rats after hypoxia–ischemia [10]. It is also unclear how immune cells gain access to the CNS. In this issue, Ek et al. show that TOLL-like receptors (TLRs) 1–4 are expressed in the choroid plexus and administration of TLR agonists—TLR2 in particular—induces a marked accumulation of white blood cells in the cerebrospinal fluid [11]. The microglia/macrophage-derived galectin-3 and quinolinic acid have been shown to be important in brain damage in experimental models. Sävman et al. demonstrate that these mediators are elevated in the cerebrospinal fluid in newborn babies after severe asphyxia and that galectin-3 levels were higher in those cases with abnormal outcome [12].

Herlenius et al. draw our attention to the perhaps less well-known clinical entity of sudden unexpected postnatal collapse of apparently healthy infants within the first days of postnatal life [13], providing a review of cases, definitions, risks, and preventive measures. They argue that adequate education of caregivers and appropriate surveillance during the first days of life should enable us to save hundreds of lives. So far, hypothermia is the only well-documented clinical therapy for combatting neonatal brain injury, and there is a need for improving the efficacy of hypothermia and development of add-on therapies. It is suggested by Olson et al. that gene expression patterns could offer guidance with regard to selection of optimal degree of cooling [14]. In a well-written review, Ramanantsoa et al. [15] propose a few critical key steps in the preclinical evaluation of add-on neuroprotectants, like for example melatonin, in the treatment of perinatal brain injury. A newly developed setup for small animal physiological and behavioral testing is described which can increase the clinical relevance of small animal studies.

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